

Vinson & Elkins

ATTORNEYS AT LAW

VINSON & ELKINS L.L.P.

THE WILLARD OFFICE BUILDING

1455 PENNSYLVANIA AVE., N.W.

WASHINGTON, D.C. 20004-1008

TELEPHONE (202) 639-6500

FAX (202) 639-6604

BEST AVAILABLE COPY

WRITER'S TELEPHONE

(202) 639-6692

December 22, 1998

RECEIVED

DEC 23 1998

The Assistant Commissioner for Patents
Washington, D.C. 20231

**PATENT EXTENSION
AC PATENTS**

BOX: Patent Ext.

Re: Application for Extension of Patent Term
Patent No.: 5,712,155
Issued: January 27, 1998
For: **DNA Encoding Tumor Necrosis Factor- Alpha
and - Beta Receptors**
Inventor(s): Smith, *et al.*
Assignee: Immunex Corporation
Atty. Dkt.: IMM200/58000

Sir:

The following documents are being forwarded herewith for appropriate action by the U.S. Patent and Trademark Office:

1. Application for Extension of Patent Term Based on Regulatory Review of a New Drug Application as Provided Under 35 U.S.C. § 156(D)(1) (in duplicate);
2. Exhibits A through D (in duplicate);
3. Our check in the amount of \$1,120.00 representing the filing fee for this application; and
4. One (1) return postcard.

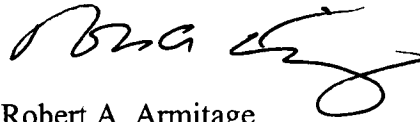
It is respectfully requested that the enclosed postpaid post card be stamped with the date the enclosed documents are received by the PTO and that it be returned as soon as possible.

The Assistant Commissioner for Patents
December 22, 1998
Page 2

The Commissioner is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 22-0365. A duplicate copy of this letter is enclosed.

Respectfully requested,

VINSON & ELKINS L.L.P.

A handwritten signature in black ink, appearing to read 'R. Armitage', with a stylized flourish at the end.

Robert A. Armitage
Attorney for Applicant
Registration No. 27,417

RAA:ct
Attachments

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 5,712,155 and the pending reissue thereof.

Issued: January 27, 1998

Inventor: Smith, Craig A., Seattle, Washington
Goodwin, Raymond G., Seattle, Washington
Beckmann, M. Patricia, Poulsbo, Washington

Assignee: Immunex Corporation, Seattle, Washington

For: DNA encoding tumor necrosis factor- alpha and receptors

RECEIVED

DEC 22 1998

**PATENT EXTENSION
A/C PATENTS**

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

**APPLICATION FOR EXTENSION OF PATENT TERM BASED ON
REGULATORY REVIEW OF A NEW DRUG APPLICATION
AS PROVIDED UNDER 35 U.S.C. § 156(D)(1)**

Sir:

Applicant, Immunex Corporation, Seattle, Washington, hereby makes application under 35 U.S.C. § 156(d)(1) and 37 C.F.R. § 1.740 for extension of the term of the reissue patent expected to be granted with respect to U.S. patent 5,712,155, filed November 29, 1994 as Ser. No. 346,555 and issued on January 27, 1988.

The patent pending reissue was originally granted a continuation of Ser. No. 523,635, filed May 10, 1990, now U.S. patent 5,395,760, which is a continuation-in-part of Ser. No. 421,417, filed October 13, 1989 now abandoned, which is a continuation-in-part of Ser. No. 405,370, filed September 11, 1989, now abandoned, which is a continuation-in-part of Ser. No. 403,241, filed September 5, 1989, now abandoned.

The current expiration date applicable to such reissue patent is March 7, 2012, based on a terminal disclaimer filed in the issued '155 patent. The extension requested is until November 2, 2012, fourteen years from the date of FDA regulatory approval, *i.e.* for a period of 240 days, or such greater or lesser period as the Commissioner may deem the applicant to be entitled. This is the maximum permitted extension provided in 35 U.S.C. § 156. The regulatory review period (reduced by one-half of the IND period) is greater than 240 days, based on the filing of applicant's CMC section of its approved Biologic License Application (BLA).

This application for extension is based on the regulatory approval of Enbrel™ Lyophilized Powder. The sole active ingredient in Enbrel™ Lyophilized Powder is etanercept, a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR II) linked to the Fc portion of human IgG1. The Fc component of etanercept contains the C_H2 domain, the C_H3 domain and hinge region, but not the C_H1 domain of IgG1. The fusion protein, etanercept, consists of 934 amino acids and exhibits an apparent molecular weight of approximately 150 kilodaltons. Etanercept is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) mammalian cell expression system.

A process for manufacturing the active ingredient in Enbrel Lyophilized Powder is claimed in the reissue application filed with respect to U.S. patent 5,712,155. The date of the BLA approval for this active ingredient is November 2, 1998. Applicant believes this is the first permitted commercial marketing or use of this active ingredient as a human drug product. This application is accordingly being made within the sixty day statutory period provided in 35 U.S.C. § 156(d).

In accordance with the provisions of 37 C.F.R. § 1.740, applicant provides the following information:

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.

Applicant submits herewith Exhibit A to this application consisting of the prescribing information as approved by the FDA. The prescribing information includes a description of the chemical structure for the active ingredient in Enbrel Lyophilized Powder. In brief, the Enbrel active ingredient is a TNFR-Fc fusion protein, as noted above. This means that the active ingredient contains two amino acid chains that form a "dimer." Each monomer of the dimer contains 467 amino acids; the dimer itself consists of 934 amino acids. Of the 467 amino acids comprising each of the monomers, 235 amino acids are the soluble form of Tumor Necrosis Factor Type II (TNFR II), commonly known as the p75 (or p80) fragment of the entire receptor. The remaining 232 amino acids of each monomer are the Fc portion of one of the known allotypes of IgG1. The Fc portion retains the "hinge" region and the second and third constant regions of the complete IgG1.

Fig 2A of the '155 patent, as reproduced below, contains the first 235 amino acids of each of the monomers comprising Enbrel's active ingredient (amino acid 1 is underlined [Leu] and amino acid 235, Asp, precedes the underlined amino acids numbered 236-248 below):

| | |
|---|-----|
| CTC TGG GCT GCG GCG CAC GCC TTG CCC GCC CAG GTG GCA TTT ACA | 177 |
| Leu Trp Ala Ala Ala His Ala Leu Pro Ala Gln Val Ala Phe Thr | 8 |
| CCC TAC GCC CCG GAG CCC GGG AGC ACA TGC CGG CTC AGA GAA TAC | 222 |
| Pro Tyr Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr | 23 |
| TAT GAC CAG ACA GCT CAG ATG TGC TGC AGC AAA TGC TCG CCG GGC | 267 |
| Tyr Asp Gln Thr Ala Gln Met Cys Cys Ser Lys Cys Ser Pro Gly | 38 |
| CAA CAT GCA AAA GTC TTC TGT ACC AAG ACC TCG GAC ACC GTG TGT | 312 |
| Gln His Ala Lys Val Phe Cys Thr Lys Thr Ser Asp Thr Val Cys | 53 |
| GAC TCC TGT GAG GAC AGC ACA TAC ACC CAG CTC TGG AAC TGG GTT | 357 |
| Asp Ser Cys Glu Asp Ser Thr Tyr Thr Gln Leu Trp Asn Trp Val | 68 |
| CCC GAG TGC TTG AGC TGT GGC TCC CGC TGT AGC TCT GAC CAG GTG | 402 |
| Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser Ser Asp Gln Val | 83 |
| GAA ACT CAA GCC TGC ACT CGG GAA CAG AAC CGC ATC TGC ACC TGC | 447 |
| Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys Thr Cys | 98 |
| AGG CCC GGC TGG TAC TGC GCG CTG AGC AAG CAG GAG GGG TGC CGG | 492 |
| Arg Pro Gly Trp Tyr Cys Ala Leu Ser Lys Gln Glu Gly Cys Arg | 113 |
| CTG TGC GCG CCG CTG CGC AAG TGC CGC CCG GGC TTC GGC GTG GCC | 537 |
| Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala | 128 |
| AGA CCA GGA ACT GAA ACA TCA GAC GTG GTG TGC AAG CCC TGT GCC | 582 |
| Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala | 143 |
| CCG GGG ACG TTC TCC AAC ACG ACT TCA TCC ACG GAT ATT TGC AGG | 627 |
| Pro Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg | 158 |
| CCC CAC CAG ATC TGT AAC GTG GTG GCC ATC CCT GGG AAT GCA AGC | 672 |
| Pro His Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser | 173 |
| ATG GAT GCA GTC TGC ACG TCC ACG TCC CCC ACC CGG AGT ATG GCC | 717 |
| Met Asp Ala Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala | 188 |
| CCA GGG GCA GTA CAC TTA CCC CAG CCA GTG TCC ACA CGA TCC CAA | 762 |
| Pro Gly Ala Val His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln | 203 |
| CAC ACG CAG CCA ACT CCA GAA CCC AGC ACT GCT CCA AGC ACC TCC | 807 |
| His Thr Gln Pro Thr Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser | 218 |
| TTC CTG CTC CCA ATG GGC CCC AGC CCC CCA GCT GAA GGG AGC ACT | 852 |
| Phe Leu Leu Pro Met Gly Pro Ser Pro Pro Ala Glu Gly Ser Thr | 233 |
| GGC GAC TTC GCT CTT CCA GTT GGA CTG ATT GTG GGT GTG ACA GCC | 897 |
| Gly Asp Phe Ala Leu Pro Val Gly Leu Ile Val Gly Val Thr Ala | 248 |
| ----- | --- |

The remaining 232 amino acids of Enbrel's active ingredient are set forth below and constitute the Fc portion of the TNFR-Fc fusion. In the chart below, the line labeled "Enbrel" represents the amino acid sequence¹ of Enbrel beginning at amino acid 205. The line labeled "IgG1" is provided for comparison and represents the amino acid sequence of one of the known IgG1 Fc sequences:

| | | | | |
|-----------------------|------------|------------|------------|------------|
| | 1205 | | 2351 | 240 |
| Enbrel [Fig. 2A Seq.] | -TQPTPE | PSTAPSTSFL | LPMGPSPPAE | GSTGDEPKSC |
| IgG1 | | | | EPKSC |
| | 241 | | | 390 |
| Enbrel | DKTHTCPPCP | APELLGGPSV | FLFPPKPKDT | LMISRTPEVT |
| IgG1 | DKTHTCPPCP | APELLGGPSV | FLFPPKPKDT | LMISRTPEVT |
| | 290 | | | 340 |
| Enbrel | PEVKFNWYVD | GVEVHNAKTK | PREEQYNSTY | RVVSVLTVLH |
| IgG1 | PEVKFNWYVD | GVEVHNAKTK | PREEQYNSTY | RVVSVLTVLH |
| | 341 | | | 390 |
| Enbrel | CKVSNKALPA | PIEKTISKAK | GQPREPQVYT | LPPSREEMTK |
| IgG1 | CKVSNKALPA | PIEKTISKAK | GQPREPQVYT | LPPSREEMTK |
| | 391 | | | 440 |
| Enbrel | GFYPSDIAVE | WESNGQPENN | YKTTTPVLDS | DGSFFLYSKL |
| IgG1 | GFYPSDIAVE | WESNGQPENN | YKTTTPVLDS | DGSFFLYSKL |
| | 441 | | 1467 | |
| Enbrel | NVFSCSVMHE | ALHNHYTQKS | LSLSPGK | |
| IgG1 | NVFSCSVMHE | ALHNHYTQKS | LSLSPGK | |

¹For convenience, amino acid codes are used. The codes used are the standard alphabetic notation for these amino acids. The coding and structure is reproduced below:

| | | |
|---------------|-------|---|
| Alanine | ala a | CH ₃ -CH (NH ₂) -COOH |
| Arginine | arg r | HN=C (NH ₂) -NH- (CH ₂) ₃ -CH (NH ₂) -COOH |
| Asparagine | asn n | H ₂ N-CO-CH ₂ -CH (NH ₂) -COOH |
| Aspartic Acid | asp d | HOOC-CH ₂ -CH (NH ₂) -COOH |
| Cysteine | cys c | HS-CH ₂ -CH (NH ₂) -COOH |
| Glutamine | gln q | H ₂ N-CO- (CH ₂) ₂ -CH (NH ₂) -COOH |
| Glutamic Acid | glu e | HOOC- (CH ₂) ₂ -CH (NH ₂) -COOH |
| Glycine | gly g | NH ₂ -CH ₂ -COOH |
| Histidine | his h | NH-CH=N-CH=C-CH ₂ -CH (NH ₂) -COOH |
| Isoleucine | ile i | CH ₃ -CH ₂ -CH (CH ₃) -CH (NH ₂) -COOH |
| Leucine | leu l | (CH ₃) ₂ -CH-CH ₂ -CH (NH ₂) -COOH |
| Lysine | lys k | H ₂ N- (CH ₂) ₄ -CH (NH ₂) -COOH |
| Methionine | met m | CH ₃ -S- (CH ₂) ₂ -CH (NH ₂) -COOH |
| Phenylalanine | phe f | Ph-CH ₂ -CH (NH ₂) -COOH |
| Proline | pro p | NH- (CH ₂) ₃ -CH-COOH |
| Serine | ser s | HO-CH ₂ -CH (NH ₂) -COOH |
| Threonine | thr t | CH ₃ -CH (OH)-CH (NH ₂) -COOH |
| Tryptophan | trp w | Ph-NH-CH=C-CH ₂ -CH (NH ₂) -COOH |
| Tyrosine | tyr y | HO-p-Ph-CH ₂ -CH (NH ₂) -COOH |
| Valine | val v | (CH ₃) ₂ -CH-CH (NH ₂) -COOH |

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The approval for Enbrel™ Lyophilized Powder was made by the Food and Drug Administration pursuant to the regulatory review provisions of section 351 of the Public Health Service Act.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.

The FDA approved for commercial marketing or use Enbrel™ Lyophilized Powder on November 2, 1998.

(4) An identification of each active ingredient in the product and a statement that each such active ingredient has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients) the use for which it was approved, and the provision of law under which it was approved.

The active ingredient in Enbrel™ Lyophilized Powder has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) A statement that the application is being submitted within the sixty-day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.

This application is being submitted on or before January 4, 1999, the last day of the sixty-day period following the November 2, 1998, NDA approval date that is not a Saturday, Sunday or holiday, as provided in Title 35, U.S.C.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.

This application for extension relates to the reissue patent expected to be granted with respect to U.S. patent 5,712,155, issued on January 27, 1998, on an application filed November 29, 1994, as a continuation of U.S. Ser. No. 523,635, filed May 10, 1990, now U.S. patent 5,395,760, which is a continuation-in-part of U.S. Ser. No. 421,417, filed October 13, 1989, now abandoned which is a continuation-in-part of U.S. Ser. No. 405,370, filed September 11, 1989 now abandoned, which is a continuation-in-part of U.S. Ser. No. 403,241, filed September 5, 1989, now abandoned. The term of this patent subsequent to March 7, 2012 has been disclaimed.

(7) A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.

A copy of the application for the reissue patent for which an extension is being sought, including the entire specification (including claims) appears in Exhibit B, together with U.S. patent 5,172,155.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.

The reissue patent for which extension is being sought has been the subject of disclaimer of the term subsequent to March 7, 2012. A copy of the disclaimer is provided as Exhibit C. The U.S. patent on which the reissue is based has not been the subject of a certificate of correction. A copy of the reissue application and the amendments made via reissue is attached as Exhibit B. The U.S. patent on which the reissue is base has not been subject to a reexamination. No maintenance fees have become due or payable as of the date of this application for extension.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product.

The approved product is the active ingredient in Enbrel™ Lyophilized Powder. Pending reissue claims 28-31, 42-45, 56-59, 70-73 and 84-87 relate to a process of manufacturing the active ingredient in Enbrel™ Lyophilized Powder.

The relationship between the reissue claims and the manufacture of the active ingredient in Enbrel™ Lyophilized Powder is set forth below:

Pending Reissue Claim

18. An isolated DNA molecule encoding a protein ***comprising a sequence of amino acids selected from the group consisting of amino acids 1-163 of FIG. 2A*** and amino acids 1-233 of FIG. 3A, wherein said protein is capable of binding TNF.

19. The isolated DNA molecule according to Claim 18, ***wherein said protein comprises amino acids 1-163 of FIG. 2A.***

Relationship to the Manufacture of the Approved Product

Fig. 2A provides a sequence of amino acids identified as +1 through +235 that is identical to an amino acid sequence contained in the active ingredient in Enbrel™ Lyophilized Powder; thus, the process of making Enbrel™ Lyophilized Powder includes using an isolated DNA encoding amino acids 1-163 of Fig. 2A.

Enbrel™ Lyophilized Powder has an active ingredient that comprises the amino acids 1-163 of Fig. 2A.

20. The isolated DNA molecule according to Claim 18, wherein *said protein comprises amino acids 1-185 of FIG. 2A.*

Enbrel™ Lyophilized Powder has an active ingredient that further comprises amino acids 1-185 of Fig. 2A.

21. The isolated DNA molecule according to Claim 18, wherein said protein *comprises amino acids 1-235 of FIG. 2A.*

Enbrel™ Lyophilized Powder has an active ingredient that further comprises amino acids 1-235 of Fig. 2A.

22. An isolated DNA molecule encoding a protein selected from the group consisting of:

Same analysis as claim 18.

(a) *a polypeptide having a sequence of amino acids comprising amino acids 1-163 of FIG. 2A;*

(b) a polypeptide having a sequence of amino acids comprising amino acids 1-233 of FIG. 3A; and

(c) a polypeptide identical to the polypeptides of (a) or (b) except for one or more modification(s) to the sequence of amino acids selected from the group consisting of: (i) inactivated N-linked glycosylation sites; (ii) altered KEX2 protease cleavage sites; and (iii) substitution or deletion of cysteine residues, wherein said protein is capable of binding TNF.

23. A recombinant expression vector comprising the DNA molecule according to Claim 18, 19, 20, 21 or 22.

Same analysis as each of claims 18-22, applied to a "vector" used to transform a host cell.

24. A host cell transformed or transfected with the recombinant expression vector according to Claim 23.

Same analysis as claim 23, applied to the "host cell" itself.

25. The host cell of Claim 24, wherein said host cell is selected from the group consisting of a microbial cell and a mammalian cell.

Enbrel™ Lyophilized Powder contains a active ingredient that can be made in a mammalian host cell.

26. The host cell of Claim 25, wherein said mammalian cell is selected from the group consisting of L cells, C127 cells, 3T3 cells, CHO cells, BHK cells and COS-7 cells.

Enbrel™ Lyophilized Powder contains an active ingredient that can be made in one or more of the mammalian cells, *i.e.*, a Chinese Hamster Ovary or CHO cell.

27. The host cell of Claim 26, wherein said mammalian cell is CHO cells.

28. A process for producing a protein capable of binding TNF, said process comprising culturing a host cell of Claim 24 under conditions suitable to effect expression of said protein.

29. The process of Claim 28, wherein said host cell is selected from the group consisting of a microbial cell and a mammalian cell.

30. The process of Claim 29, wherein said mammalian cell is selected from the group consisting of L cells, C127 cells, 3T3 cells, CHO cells, BHK cells and COS-7 cells.

31. The process of Claim 30, wherein said mammalian cell is CHO cells.

Enbrel™ Lyophilized Powder contains an active ingredient that can be made in a CHO cell.

Enbrel™ Lyophilized Powder contains an active ingredient that involves culturing a host cell that has been transformed or transfected with a recombinant expression vector that utilizes an isolated DNA molecule that encodes an amino acid sequence that includes amino acids 1-163, 1-185 and 1-235 of Fig. 2A.

Same analysis as claim 25.

Same analysis as claim 26.

Same analysis as claim 27.

32. An isolated DNA molecule encoding a soluble TNF receptor protein comprising a sequence of *amino acids selected from the group consisting of from about amino acid 1 to about amino acid 163 of FIG. 2A* and from about amino acid 1 to about amino acid 233 of FIG. 3A, wherein said soluble TNF receptor protein is capable of binding TNF protein.

33. The isolated DNA molecule according to Claim 32, wherein said soluble TNF receptor protein comprises *from about amino acid 1 to about amino acid 163 of FIG. 2A*.

34. The isolated DNA molecule according to Claim 32, wherein said soluble TNF receptor protein comprises *from about amino acid 1 to about amino acid 185 of FIG. 2A*.

35. The isolated DNA molecule according to Claim 32, wherein said TNF soluble receptor protein comprises *from about amino acid 1 to about amino acid 235 of FIG. 2A*.

36. An isolated DNA molecule encoding a soluble TNF receptor protein selected from the group consisting of:

(a) a TNF receptor polypeptide having a sequence of amino acids comprising *from about amino acid 1 to about amino acid 163 of FIG. 2A*;

(b) a TNF receptor polypeptide having a sequence of amino acids comprising from about amino acid 1 to about amino acid 233 of FIG. 3A; and

(c) a TNF receptor polypeptide identical to the TNF receptor polypeptides of (a) or (b) except for one or more modification(s) to the sequence of amino acids selected from the group consisting of: (i) inactivated N-linked glycosylation sites; (ii) altered KEX2 protease cleavage sites; and (iii) substitution or deletion of cysteine residues, wherein said soluble TNF receptor protein is capable of binding TNF.

For claims 32-45, see the analysis above for claims 18-31, respectively. In each case, the active ingredient in Enbrel™ Lyophilized Powder has about 163, 185, or 235 amino acids as set forth in Fig. 2A.

37. A recombinant expression vector comprising the DNA molecule according to Claim 32, 33, 34, 35 or 36.

38. A host cell transformed or transfected with the recombinant expression vector according to Claim 37.

39. The host cell of Claim 38, wherein said host cell is selected from the group consisting of a microbial cell and a mammalian cell.

40. The host cell of Claim 39, wherein said mammalian cell is selected from the group consisting of L cells, C127 cells, 3T3 cells, CHO cells, BHK cells and COS-7 cells.

41. The host cell of Claim 40, wherein said mammalian cell is CHO cells.

42. A process for producing a protein capable of binding TNF, said process comprising culturing a host cell of Claim 38 under conditions suitable to effect expression of said protein.

43. The process of Claim 42, wherein said host cell is selected from the group consisting of a microbial cell and a mammalian cell.

44. The process of Claim 43, wherein said mammalian cell is selected from the group consisting of L cells, C127 cells, 3T3 cells, CHO cells, BHK cells and COS-7 cells.

45. The process of Claim 44, wherein said mammalian cell is CHO cells.

46. An isolated DNA molecule encoding a soluble TNF receptor protein comprising a sequence of *amino acids selected from the group consisting of from amino acid 1 to amino acid 163 of FIG. 2A* and from amino acid 1 to amino acid 233 of FIG. 3A, wherein said soluble TNF receptor protein is capable of binding TNF protein.

47. The isolated DNA molecule according to Claim 46, wherein said soluble TNF receptor protein *comprises from amino acid 1 to amino acid 163 of FIG. 2A.*

For claims 46-59, see the analysis above for claims 18-31, respectively. In each case, the active ingredient in Enbrel™ Lyophilized Powder has the 163, 185, or 235 amino acids as set forth in Fig. 2A and is a soluble TNF receptor protein.

48. The isolated DNA molecule according to Claim 46, wherein said soluble TNF receptor protein *comprises from amino acid 1 to amino acid 185 of FIG. 2A.*

49. The isolated DNA molecule according to Claim 46, wherein said soluble TNF receptor protein *comprises from amino acid 1 to amino acid 235 of FIG. 2A.*

50. An isolated DNA molecule encoding a soluble TNF receptor protein selected from the group consisting of:

(a) a TNF receptor polypeptide having a sequence of amino acids *comprising from amino acid 1 to amino acid 163 of FIG. 2A;*

(b) a TNF receptor polypeptide having a sequence of amino acids comprising from amino acid 1 to amino acid 233 of FIG. 3A; and

(c) a TNF receptor polypeptide identical to the TNF receptor polypeptides of (a) or (b) except for one or more modification(s) to the sequence of amino acids selected from the group consisting of: (i) inactivated N-linked glycosylation sites; (ii) altered KEX2 protease cleavage sites; and (iii) substitution or deletion of cysteine residues, wherein said soluble TNF receptor protein is capable of binding TNF. The isolated DNA molecule according to Claim 32, wherein said soluble TNF receptor protein comprises *from about amino acid 1 to about amino acid 163 of FIG. 2A.*

51. A recombinant expression vector comprising the DNA molecule according to Claim 46, 47, 48, 49 or 50.

52. A host cell transformed or transfected with the recombinant expression vector according to Claim 51.

53. The host cell of Claim 52, wherein said host cell is selected from the group consisting of a microbial cell and a mammalian cell.

54. The host cell of Claim 53, wherein said mammalian cell is selected from the group consisting of L cells, C127 cells, 3T3 cells, CHO cells, BHK cells and COS-7 cells.

55. The host cell of Claim 54, wherein said mammalian cell is CHO cells.

56. A process for producing a protein capable of binding TNF, said process comprising culturing a host cell of Claim 52 under conditions suitable to effect expression of said protein.

57. The process of Claim 56, wherein said host cell is selected from the group consisting of a microbial cell and a mammalian cell.

58. The process of Claim 57, wherein said mammalian cell is selected from the group consisting of L cells, C127 cells, 3T3 cells, CHO cells, BHK cells and COS-7 cells.

59. The process of Claim 58, wherein said mammalian cell is CHO cells.

60. An isolated DNA molecule encoding a protein comprising a sequence of amino acids selected from the group *consisting of amino acids 1-163 of FIG. 2A* and amino acids 1-233 of FIG. 3A, *wherein said protein lacks amino acids 236-265 of FIG. 2A* and amino acids 234-265 of FIG. 3A, respectively, and wherein said protein is capable of binding TNF.

61. The isolated DNA molecule according to Claim 60, wherein said protein *comprises amino acids 1-163 of FIG. 2A*.

62. The isolated DNA molecule according to Claim 60, wherein said protein *comprises amino acids 1-185 of FIG. 2A*.

63. The isolated DNA molecule according to Claim 60, wherein said protein *comprises amino acids 1-235 of FIG. 2A*.

64. An isolated DNA molecule encoding a protein selected from the group consisting of:

(a) a TNF receptor polypeptide having a sequence of amino acids *comprising amino acids 1-163 of FIG. 2A*, wherein said polypeptide *lacks amino acids 236-265 of FIG. 2A*;

(b) a TNF receptor polypeptide having a sequence of amino acids comprising amino acids 1-233 of FIG. 3A, wherein said polypeptide lacks amino acids 234-265 of FIG. 3A; and

(c) a TNF receptor polypeptide identical to the TNF receptor polypeptides of (a) or (b) except for one or more modification(s) to the sequence of amino acids selected from the group consisting of: (i) inactivated N-linked glycosylation sites; (ii) altered KEX2 protease cleavage sites; and (iii) substitution or deletion of cysteine residues, wherein said protein is capable of binding TNF.

65. A recombinant expression vector comprising the DNA molecule according to Claim 60, 61, 62, 63 or 64.

For claims 60-73, see the analysis above for claims 18-31, respectively. In each case, the active ingredient in Enbrel™ Lyophilized Powder has the 163, 185, or 235 amino acids as set forth in Fig. 2A and lacks amino acids 236-265.

66. A host cell transformed or transfected with the recombinant expression vector according to Claim 65.

67. The host cell of Claim 66, wherein said host cell is selected from the group consisting of a microbial cell and a mammalian cell.

68. The host cell of Claim 67, wherein said mammalian cell is selected from the group consisting of L cells, C127 cells, 3T3 cells, CHO cells, BHK cells and COS-7 cells.

69. The host cell of Claim 68, wherein said mammalian cell is CHO cells.

70. A process for producing a protein capable of binding TNF, said process comprising culturing a host cell of Claim 67 under conditions suitable to effect expression of said protein.

71. The process of Claim 70, wherein said host cell is selected from the group consisting of a microbial cell and a mammalian cell.

72. The process of Claim 71, wherein said mammalian cell is selected from the group consisting of L cells, C127 cells, 3T3 cells, CHO cells, BHK cells and COS-7 cells.

73. The process of Claim 72, wherein said mammalian cell is CHO cells.

74. An isolated DNA molecule encoding a protein comprising a sequence of amino acids selected from the group *consisting of amino acids 1-163 of FIG. 2A* and amino acids 1-233 of FIG. 3A, *wherein said protein lacks a functional transmembrane region*, and wherein said protein is capable of binding TNF.

75. The isolated DNA molecule according to Claim 74, wherein said protein *comprises amino acids 1-163 of FIG. 2A*.

76. The isolated DNA molecule according to Claim 74, wherein said protein *comprises amino acids 1-185 of FIG. 2A*.

77. The isolated DNA molecule according to Claim 74, wherein said protein *comprises amino acids 1-235 of FIG. 2A*.

78. An isolated DNA molecule encoding a protein selected from the group consisting of:

(a) a TNF receptor polypeptide having a sequence of amino acids *comprising amino acids 1-163 of FIG. 2A*;

(b) a TNF receptor polypeptide having a sequence of amino acids comprising amino acids 1-233 of FIG. 3A; and

(c) a TNF receptor polypeptide identical to the TNF receptor polypeptides of (a) or (b) except for one or more modification(s) to the sequence of amino acids selected from the group consisting of: (i) inactivated N-linked glycosylation sites; (ii) altered KEX2 protease cleavage sites; and (iii) substitution or deletion of cysteine residues, wherein said protein lacks a functional transmembrane region; and wherein said protein is capable of binding TNF.

79. A recombinant expression vector comprising the DNA molecule according to Claim 74, 75, 76, 77 or 78.

80. A host cell transformed or transfected with the recombinant expression vector according to Claim 79.

For claims 74-87, see the analysis above for claims 18-31, respectively. In each case, the active ingredient in Enbrel™ Lyophilized Powder has the 163, 185, or 235 amino acids as set forth in Fig. 2A and lacks a functional transmembrane region.

81. The host cell of Claim 80, wherein said host cell is selected from the group consisting of a microbial cell and a mammalian cell.

82. The host cell of Claim 81, wherein said mammalian cell is selected from the group consisting of L cells, C127 cells, 3T3 cells, CHO cells, BHK cells and COS-7 cells.

83. The host cell of Claim 82, wherein said mammalian cell is CHO cells.

84. A process for producing a protein capable of binding TNF, said process comprising culturing a host cell of Claim 80 under conditions suitable to effect expression of said protein.

85. The process of Claim 84, wherein said host cell is selected from the group consisting of a microbial cell and a mammalian cell.

86. The process of Claim 85, wherein said mammalian cell is selected from the group consisting of L cells, C127 cells, 3T3 cells, CHO cells, BHK cells and COS-7 cells.

87. The process of Claim 86, wherein said mammalian cell is CHO cells.

10. A statement beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period, particularly, for a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued.

For the Biological License Application (BLA) Approval of Enbrel™ Lyophilized Powder the following are the applicable dates:

| | |
|---------------------------|--|
| Effective date for IND | June 26, 1992 |
| Initial Submission of BLA | March 9, 1998 for Chemistry, Manufacturing and Controls (CMC) portion of the BLA, and June 22, 1998 for acceptance of the completed BLA. |
| FDA Approval for BLA | November 2, 1998 |

(11) A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

The regulatory review period began on January 27, 1998, with the issuance of the '155 patent. During the period beginning on January 27, 1998 and continuing through November 2, 1998, efforts were underway to complete the Biological License Application (BLA), which was filed in stages beginning on March 9, 1998:

| | |
|----------------|--|
| 4/30/92 | Pre-IND Meeting- Use of Enbrel for sepsis syndrome |
| 5/28/92 | Submission of BB-IND 4571 (Sepsis)- (includes Protocol 9125) |
| 6/26/92 | <i>Effective date for BB-IND 4571</i> |
| 8/26/92 | Submission of Protocol 9203 (BB-IND 4571) |
| 3/8/93 | BB-IND 4571- Amendment for transfer of manufacture of Enbrel |
| 4/27/93 | BB-IND 5088 (Arthritis)- (includes Protocols 16.0002, 16.0003) |
| 4/28/93 | BB-IND 5089 (HIV-1 Infection)- (includes Protocol 16.11001) |
| 5/26/93 | Effective date for BB-IND 5088 |
| 10/11/93 | Effective date for BB-IND 5289 (Crohn's Disease)- (includes Protocol 16.0005) |
| 11/12/93 | Effective date for BB-IND 5298 |
| 6/3/94 | Submission of Protocol 16.0004 (BB-IND 5088) |
| 4/5/95 | BB-IND 4571- Amendment for scale-up- 300L scale-1600L scale |
| 6/2/95 | Submission of Protocol 16.0006 (BB-IND 5289) |
| 2/20/96 | Submission of Protocol 16.0008 (BB-IND 5088) |
| 4/26/96 | Submission of Protocol 16.0010 BB-IND 5088) |
| 5/7/96 | End of Phase II Meeting- review of proposed clinical studies for rheumatoid arthritis |
| 7/1/96 | Submission of Protocol 16.0009 (BB-IND 5088) |
| 2/6/97 | Submission of Protocol 16.0012 (BB-IND 5088) |
| 3/11/97 | End of Phase II Meeting - to discuss Immunex's proposed study of Enbrel in pediatric patients with juvenile rheumatoid arthritis (JRA) |
| 4/17/97 | Submission of Protocol 16.0014 (BB-IND 5088) |
| 4/21/97 | Submission of Protocol 16.0018 (BB-IND 5088) |
| 6/13/97 | Submission of Protocol 16.0016 (BB-IND 5088) |
| 6/13/97 | Submission of Protocol 16.0017 (BB-IND 5088) |
| 6/13/97 | Submission of Protocol 16.0019 (BB-IND 5088) |
| 6/17/97 | PM-BLA Meeting to discuss Chemistry, Manufacturing and Controls (CMC) issues |
| 10/20/97 | BB-IND 45 17- Amendment for Manufacture of Enbrel |
| 12/2/97 | Pre-BLA Meeting- Presented the results from Immunex's Phase III clinical studies |
| 1/22/98 | Request for Fast track Designation for Enbrel in Rheumatoid Arthritis |
| 3/9/98 | Submission of CMC Section of BLA |
| 4/13/98 | Submission of Pharmacokinetic/Toxicology Section of ELA |
| 5/7/98 | Submission of Clinical Section of BLA |
| 6/15/98 | Request for Orphan Drug Status (JRA)- Approved for Orphan Drug |
| 6/22/98 | <i>BLA accepted for filing</i> |
| 9/2/98 | Submission of IND 7905 for use of Enbrel for Chronic Heart Failure (CHF) |
| 9/16/98 | Arthritis Advisory Committee (ACC) Meeting |
| 11/2/98 | <i>BLA approved for the use of Enbrel for treatment of rheumatoid arthritis</i> |

(12) A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.

Applicant believes that it is entitled to an extension for U.S. patent 5,712,155 in accordance with the provisions of 35 U.S.C. § 156. Applicant believes that the period of extension applicable to the patent is 240 days, based on the following chronology. For completeness, applicant has included an alternative calculation based on the acceptance of the BLA by the FDA.

| Patent Extension Calculation | Calculations (BLA Acceptance) |
|--|--|
| Date IND Becomes Effective | June 26, 1992 |
| Date BLA Submitted to the FDA | May 7, 1998 |
| Date BLA Approved by the FDA | November 2, 1998 |
| Patent Issue Date | January 27, 1998 |
| U.S. Non-provisional Effective Patent Filing Date | September 5, 1989 |
| U.S. Non-provisional Actual Patent Filing Date | November 29, 1994 |
| Patent Terminal Disclaimer Date (As Applicable) | March 7, 2012 |
| 17 Years from Issue Date | January 27, 2015 |
| 20 Years from Filing Date | September 5, 2009 |
| Greater of 17 Years from Issue or 20 Years from Filing | January 27, 2015 |
| Pre-GATT Term, If Applicable and Longer | January 27, 2015 |
| Actual Patent Term (Including Applicable Disclaimer) | March 7, 2012 |
| Start Date of Regulatory Review Period | January 27, 1998 |
| IND Review Period (days) | 101 |
| ½ IND Review Period (days) | 51 |
| BLA Review Period (days) | 180 |
| Regulatory Review Period (days) | 281 |
| BLA Period + ½ IND Period (days) | 231 |
| Expiration Date of 5 Year Limitation Period | March 7, 2017 |
| Five Year Limitation Period in Days | 1,826 |
| Maximum Extension Period Before 14 Year Limit | 231 |
| Expiration Date Before Applying 14 Year Limit | October 23, 2012 |
| Expiration of 14 Years from BLA Approval | November 2, 2012 |
| Expiration Date Applying 14 Year Limit | October 23, 2012 |
| Statutory Extension Period in Days | 231 |

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (see 37 C.F.R. § 1.765).

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension (see 37 C.F.R. § 1.20(j)).

Applicant hereby encloses a check in the amount of the prescribed fee under 37 C.F.R. § 1.20(j), \$1,120.00. If for any reason this payment is insufficient, applicant hereby authorizes that any deficiency may be charged to Deposit Account 22-0365.

(15) The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed.

Please direct all correspondence in connection with this application to:

Robert A. Armitage
Registration No: 27,417
Vinson & Elkins, L.L.P.
Suite 700
1455 Pennsylvania Avenue, N.W.
Washington, D.C. 20004-1008
Telephone: (202)639-6692
Facsimile: (202)639-6604.

(16) A duplicate of the application papers, certified as such.

Applicant hereby certifies that this application for extension is being filed in duplicate.

(17) An oath or declaration.

Applicant, through its undersigned patent attorney authorized to practice before the Patent and Trademark Office and who has general authority from the owner to act on behalf of the owner in patent matters, being duly warned that willful false statements are punishable by fine or imprisonment or both under section 1001 of Title 18, United States Code and that willful false statements and the like may jeopardize the validity of this application and the patent to which it relates, states and declares that the following statements made based on his own knowledge are true and that all statements made on information and belief are believed to be true:

(1) The undersigned is registered to practice before the Patent and Trademark Office and is making this declaration as a patent attorney who has general authority to act on behalf of the applicant in patent matters.

(2) The undersigned has reviewed and understands the contents of the application being submitted pursuant to this section;

(3) The undersigned believes the patent is subject to extension pursuant to 37 C.F.R. § 1.710;

(4) The undersigned believes an extension of the length claimed is justified under 35 U.S.C. 156 and the applicable regulations; and

(5) The undersigned believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.


If this application for extension of patent term is held to be informal, applicant may seek to have that holding reviewed by filing a petition with the required fee, as necessary, pursuant to 37 C.F.R. §§ 1.181, 1.182 or 1.183, as appropriate, within such time as may be set in any notice that the application has been held to be informal, or if no time is set, within one month of the date on which the application was held informal.

Applicant is providing herewith in Exhibit D a power of attorney and general authority for the undersigned to execute this application and make the declaration as provided in item (17) above.

Respectfully submitted,

Immunex Corporation

By:


Robert A. Armitage, Registration Number 27,417
Vinson & Elkins, L.L.P.
Suite 700
1455 Pennsylvania Avenue, N.W.
Washington, D.C. 20004-1008
Telephone: (202)639-6692
Facsimile: (202)879-8892
Email: RArmitage@velaw.com.

Attachments:

Check for \$1,120.00

Exhibit A — Enbrel™ Lyophilized Powder prescribing information as approved by the FDA.

Exhibit B — Copy of U.S. patent 5,712,155 and the pending reissue application for patent based thereon.

Exhibit C — Copy of terminal disclaimer related to U.S. patent 5,712,155.

Exhibit D — Power of Attorney and General Authority from Assignee.